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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,488	02/16/2000	MAURICE MOLONEY	9369-98	6010

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EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	26

DATE MAILED: 03/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,488	MOLONEY ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-20 and 24-27* is/are pending in the application.

4a) Of the above claim(s) *31-40 and 45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-20,24-26,28-30 and 41-44* is/are rejected.

7)☒ Claim(s) *27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Application Status

[1] In view of new rejections under 35 USC 112, second paragraph, 35 USC 102(b), and 35 USC 103(a), the finality of the rejection of the last Office action is withdrawn.

[2] Claims 1, 4-20, and 24-47 are pending in the application.

[3] Claims 31-40 and 45-47 are withdrawn from consideration as being drawn to a non-elected invention.

[4] Applicant's amendment to claims 1, 6, 13-16, 20, 25, 41, 42, and 44 and cancellation of claim 23 in Paper No. 24, filed 02/04/03, is acknowledged.

[5] It is noted that in a telephone conversation with Ms. Micheline Gravelle on 03/03/03, it was noted that claims 20, 41, and 42 had been amended in Paper No. 21 to remove the limitation "wherein the heterologous nucleic acid sequence is located immediately downstream of the nucleic acid sequence encoding the chymosin pro-peptide". Ms. Gravelle indicated that this was an editing error and that the limitation as described above should have remained in the claims. Thus, in the interest of advancing prosecution, the claims have been examined as though the limitation as stated above were present in claims 20, 41, and 42.

[6] Applicant's arguments in Paper No. 24 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[7] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Specification/Informalities

[8] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Method for Producing and

Cleaving a Fusion Protein with an N-Terminal Chymosin Pro-Peptide". See MPEP § 606.01 regarding examiner's change in title.

Claim Objection(s)

[9] Claim 27 is objected to in the use of "SEQ.ID.NO". Sequences should be identified using the proper sequence identifier "SEQ ID NO:". Appropriate correction is required.

Claim Rejection(s) - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[10] Claim 42 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claim 42 is drawn to a food composition comprising a chimeric nucleic acid sequence encoding a fusion protein comprising: a) a nucleic acid encoding a chymosin pro-peptide and b) a nucleic acid encoding a polypeptide heterologous to the chymosin pro-peptide, wherein the heterologous nucleic acid sequence is located immediately downstream of the nucleic acid sequence encoding the chymosin pro-peptide.

While the examiner *can* find an asserted utility for a food composition comprising the protein expressed from the chimeric nucleic acid (see page 13, lines 27-34 of the instant specification), the examiner can find no asserted utility for a food composition comprising said chimeric nucleic acid and there appears to be no well-established utility for such. One of ordinary skill in the art would recognize that *any* nucleic acid could be included as a food composition. However, such a nucleic acid, when ingested, would be degraded and the nutritional value of the claimed nucleic acid would be no greater

than any other nucleic acid. Thus, even if a utility for said food composition were asserted, this utility would not be a *specific* utility.

Claim Rejection(s) - 35 USC § 112, Second Paragraph

[11] Claims 4, 5, 7-14, 19, 24-27, 43, and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 5, 7-14, 19, 24-30, 43, and 44 are indefinite in the recitation of "A method" (claims 4, 5, 7-14, and 19) "A chimeric nucleic acid" (claims 24-27), "a chimeric nucleic acid" (claim 28), "an expression vector" (claims 29 and 30), and "A composition" (claims 43 and 44). It is suggested that the terms be replaced with definite terms as follows: replace "A method" with "The method" in claims 4, 5, 7-14, and 19; replace "A chimeric nucleic acid" with "The chimeric nucleic acid" in claims 24-27; replace "a chimeric nucleic acid" with "the chimeric nucleic acid in claim 28; replace "an expression vector" with "the expression vector" in claims 29 and 30; and replace "A composition" with "The composition" in claims 43 and 44.

Claim Rejection(s) - 35 USC § 112, First Paragraph

[12] Claim 42 is rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above (see item 10 of the instant Office action), one skilled in the art clearly would not know how to use the claimed invention.

[13] The scope of enablement rejection of claims 7, 11, 12, 17, and 18 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see, e.g., item 9 of Paper No. 15). Regarding claim 7, the specification, while being enabling for the method of claim 1, further comprising altering the pH to a pH between 2 to 7, does not reasonably provide enablement for the method of claim 1, further comprising altering the pH, salt concentration, or temperature to *any* pH, salt concentration, or temperature.

Regarding claims 11, 12, 17, and 18, the specification, while being enabling for the method of claims 10 or 16, wherein the in vivo conditions are in milk, the stomach, or the gut of an animal, does not reasonably provide enablement for the method of claims 10 or 16, wherein the in vivo conditions are those prevalent in any tissue or bodily fluid of an animal and optionally wherein the tissue of bodily fluid comprises blood or kidneys. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Undue experimentation would be required for a skilled artisan to make the entire scope of claimed methods. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). The Factors most relevant to the instant rejection are addressed below.

- The claims are overly broad in scope: The specification does not provide enablement for the broad scope of the claims, including the method of claim 1, further comprising altering the pH, salt concentration, or temperature to *any* pH, salt concentration, or temperature (claim 7) or the method of claims 10 or 16, wherein the in vivo conditions are those prevalent in any tissue or bodily fluid of an animal and optionally wherein the tissue of bodily fluid comprises blood or kidneys (claims 11, 12, 17, and 18). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large range of pH, salt concentration, or temperature values and tissues and bodily fluids broadly encompassed by the claims of which the methods of claims 7, 11, 12, 17, and 18 can be practiced. In this case, the specification is enabling only for the method of claim 1, further comprising altering the pH to a pH between 2 to 7 (claim 7) or the method of claims 10 or 16, wherein the in vivo conditions are in milk, the stomach, or the gut of an animal (claims 11, 12, 17, and 18).

- The lack of guidance and working examples: Regarding altered pH, salt concentration, and temperature conditions, the specification provides guidance for altered pH conditions in the form of two working examples, i.e., a method of producing a GST—chymosin pro-peptide—hirudin polypeptide cleavable by treatment with chymosin at pH 4.5 (pages 14 and 15) or a His tag—chymosin pro-peptide—carp growth hormone polypeptide cleavable by treatment with chymosin at pH 2 (page 17, top) or red turnip beetle gut extract (page 17 bottom). Also, the prior art indicates that *Mucor pusillus* rennin (MPR) is active at a pH of as high as 7 and as low as 2 (Hiramatsu et al. *J Biol Chem* 264:16865). The specification and the prior art fail to provide guidance for practicing the method of claim 1 at any pH, salt concentration, or temperature and a skilled artisan would recognize that extreme ranges of pH, salt concentration, and/or temperature denatures and/or inactivates an enzyme's activity. Regarding the tissue and bodily fluids, while it is known in the art that chymosin and other aspartic proteases are abundant in the digestive tract of certain animals, there is no indication that chymosin is present in all bodily tissues or fluids and the specification fails to provide guidance regarding which aspartic proteases are expressed in which tissues. While the state of the art is sufficient to enable a skilled artisan to express an aspartic protease in the milk of an animal such as a cow or goat, the state of the art does not enable expression of a transgene in *any* tissue or bodily fluid, particularly kidney and blood. Furthermore, such expression may be deleterious to an organism and in this regard, guidance has not been provided in the specification.
- The high degree of unpredictability of the art: One of skill in the art would recognize that, based on the lack of guidance provided by the specification and the prior art, a high degree of unpredictability exists for practicing the method of claim 1 using any altered pH, salt concentration, or temperature or in any tissue or bodily fluid optionally wherein the tissue is kidney and bodily fluid is blood.
- The amount of experimentation: Due to the lack of guidance and high degree of unpredictability, a skilled artisan would recognize the undue amount of experimentation that would be required to make the entire scope of the claimed methods.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants argue (beginning at the bottom of page 7 of Paper No. 24) that a skilled artisan could readily identify those conditions that achieve cleavage once the aspartic protease to be added to assist cleavage is selected. Applicant argues the optimum pH and other conditions required to achieve cleavage with various aspartic proteases are well-known and readily available to one of skill in the art. Applicant's arguments are not found persuasive. The claims are not limited to those pH conditions that optimal for cleavage. Instead, the claims are so broad as to encompass the method of claim 1 practiced under any pH, salt concentration, or temperature and, as stated above, a skilled artisan would clearly recognize that a determination of those conditions would constitute undue experimentation.

Claim Rejection(s) - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[14] Claims 20, 25, 26, 28, 29, 30, 41, 43, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Hiramatsu et al. (*Appl Environ Microbiol* (1990) 56:2125-2132, hereafter referred to as "Hiramatsu et al. (1990)" to avoid confusion with references to an additional Hiramatsu et al. reference as cited below). Claim 20 is drawn to a chimeric nucleic acid sequence encoding a fusion protein

comprising: a) a nucleic acid encoding a chymosin pro-peptide and b) a nucleic acid encoding a polypeptide heterologous to the chymosin pro-peptide, wherein the heterologous nucleic acid sequence is located immediately downstream of the nucleic acid sequence encoding the chymosin pro-peptide and claim 41 is drawn to a composition comprising said chimeric nucleic acid. Claim 25 is drawn to the chimeric nucleic acid of claim 20, which does not include a coding sequence for a mature form of chymosin. Claims 26 and 43 limit the nucleic acid of claims 20 and 41, respectively, to DNA sequences. Claim 28 is drawn to an expression vector comprising the nucleic acid of claim 20. Claim 29 is drawn to a host cell comprising the vector of claim 28 and claim 30 further limits the cell type of claim 29. It is noted that the term "pro-peptide" has been defined in the specification as "the amino terminal portion of a zymogen or a functional portion thereof up to the maturation site" (page 5, lines 24 and 25 of the instant specification) and the term "heterologous polypeptide" has been defined in the specification as "any polypeptide that is heterologous to the pro-peptide, meaning that it is not the mature protein that is normally associated with the pro-peptide as a zymogen" (page 5, lines 31-33 of the instant specification).

Hiramatsu et al. (1990) teach secretion of human growth hormone (hGH) using various fragments of *Mucor pusillus* rennin (MPR) prepro-peptide as leader sequences for secretion (page 2125, right column top). Hiramatsu et al. (1990) teach expression vectors JGH1, JGH4, and JGH5 comprising a nucleic acid encoding a fusion protein having a full-length MPR pre-peptide and a five amino acid amino-terminal fragment of an MPR pro-peptide linked to hGH via a three amino acid linker peptide (see page 2128, Figure 2 parts a) and b) and page 2129, Figure 4). It is noted that the terms rennin and chymosin are used synonymously in the art to refer to the same enzyme, i.e., chymosin = rennin. The vectors of JGH2, JGH4, and JGH5 have an upstream promoter and a downstream terminator sequence relative to the nucleic acid encoding the fusion protein (page 2128, Figure 2 part a) and page 2129, Figure 4). Hiramatsu et al. (1990) teach *Saccharomyces cerevisiae* strain MC16 was transformed with vectors JGH1, JGH4, and JGH5 (page 2126, left column, middle and page 2127, right column). This anticipates claims 20, 25, 26, 28, 29, 30, 41, 43, and 44 as written.

Claim Rejection(s) - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[15] Claims 1, 4, 6-10, 13-16, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hiramatsu et al. (1990) in view of Hiramatsu (*J Biol Chem* (1989) 264:16862-16866; hereafter referred to as "Hiramatsu et al. (1989)"). Claim 1 is drawn to a method for the preparation of a polypeptide comprising: a) transforming a host with an expression vector comprising: 1) a nucleic acid capable of regulating transcription in the host, operatively linked to 2) a chimeric nucleic acid sequence encoding a fusion protein comprising: a) a nucleic acid encoding a chymosin pro-peptide and b) a nucleic acid encoding a polypeptide heterologous to the chymosin pro-peptide, wherein the heterologous nucleic acid sequence is located immediately downstream of the nucleic acid sequence encoding the chymosin pro-peptide; operatively linked to 3) a nucleic acid encoding a termination region, b) growing the host to produce the fusion protein; and c) adding a mature form of an autocatalytically maturing aspartic protease that is capable of cleaving the chymosin pro-peptide, to the fusion protein so that the pro-peptide is cleaved from the fusion protein to release the polypeptide. Claim 4 limits the aspartic protease. Claim 6 limits the nucleic acid sequence to not including a sequence encoding a mature form of chymosin. Claims 7 and 8 (in relevant part) are drawn to the method of claim 1 further comprising altering the pH. Claims 9 and 10 limit the method of claim 1 to taking place under in vitro or in vivo conditions, respectively. Claims 13 and 14 limit the aspartic protease of claim 1 to chymosin or an aspartic protease heterologous to the chymosin pro-peptide. Claims 15 and 16 limit the method of claim 13 to adding the chymosin under in vitro or in vivo conditions. Claim 19 limits the nucleic acid of the method of claim 1 to DNA.

Hiramatsu et al. (1990) disclose the teachings as described in item 14 above. Relevant to the instant rejection, Hiramatsu et al. (1990) also teach the use of vectors JGH2, JGH4, and JGH5 for a method of producing a fusion protein comprising a full-length MPR pre-peptide and five amino-terminal amino acids of the MPR pro-peptide fused to hGH via a three amino acid linker. *S. cerevisiae* strain MC16 was transformed with vector JGH2 (page 2125, right column and page 2126, left column) for use as a host cell for fusion protein expression. Hiramatsu et al. (1990) teach that removal of the MPR pro-peptide component of the MPR-hGH fusion protein expressed from vector JGH2 is required to obtain hGH with the same amino-terminus as native hGH (page 2131, left column, bottom). Hiramatsu et al. (1990) suggest that removal of these additional amino acids may be achieved by introducing an artificial cleavage site such as Factor Xa, just before the hGH sequence (page 2131, left column, bottom). Hiramatsu et al. (1990) do not teach using an aspartic protease to cleave the amino-terminal MPR pro-peptide component from their expressed fusion protein.

Hiramatsu et al. (1989) teach expression of pro-MPR (MPR with its full-length pro-peptide) using *S. cerevisiae* strain MC16 transformed with vector JP1 (page 16863) and subsequent cleavage of the pro-peptide component from the mature MPR component, i.e., conversion of pro-MPR to MPR, autocatalytically (page 16864, right column) or by reducing the pH to as low as 2.0 (page 16863, left and right columns and page 16864, left column) in the culture medium. Hiramatsu et al. demonstrate that a protease other than MPR contributed to pro-MPR to MPR conversion and provide results indicating that the protease is proteinase A (page 16865, left column). Hiramatsu et al. (1989) teach the amino acid sequence at the junction of the pro-peptide and mature MPR (page 16864, Figure 4).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Hiramatsu et al. (1990) and Hiramatsu et al. (1989) for a method of producing hGH using the vector of JGH2 with the nucleic acid encoding the five amino acid amino-terminal pro-peptide fragment replaced with a *full-length* MPR pro-peptide including an MPR pro-peptide-mature MPR cleavage site at the pro-peptide-hGH junction. By including the *full-length* MPR pro-peptide including an MPR pro-peptide-mature MPR cleavage site at the pro-peptide-hGH junction, one of skill in the art would

have recognized that the pro-peptide would be cleaved by the expressed MPR or endogenous yeast proteinase A, thus Factor Xa cleavage of the pro-peptide from the hGH component would not be required. One would have been motivated for a method for producing hGH using vector JGH2 and replacing the nucleic acid sequence encoding the five amino acid amino-terminal MPR pro-peptide fragment with a nucleic acid encoding the full-length pro-peptide including an MPR pro-peptide-mature MPR cleavage site at the pro-peptide-hGH junction in order to cleave the pro-peptide leader sequence from the hGH in the medium by MPR or yeast proteinase A as cleavage of the pro-peptide leader from hGH using enzymes expressed by the host cell would not require an additional step requiring Factor Xa cleavage. One of skill in the art, based on the teachings of Hiramatsu et al. (1989), would have recognized that the pro-peptide including an MPR pro-peptide-mature MPR cleavage site at the pro-peptide-hGH junction would be cleaved by MPR or endogenous proteinase A without an additional step requiring Factor Xa cleavage. One would have a reasonable expectation of success for a method of producing hGH using the vector of JGH2 with the nucleic acid encoding the five amino acid amino-terminal pro-peptide fragment replaced with a *full-length* MPR pro-peptide including an MPR pro-peptide-mature MPR cleavage site at the pro-peptide-hGH junction. Therefore, claims 1, 4, 6-10, 13-16, and 19, drawn to the methods of producing a recombinant protein as described above, would have been obvious to one of ordinary skill in the art.

[16] Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hiramatsu et al. (1990) in view of Hiramatsu (1989) as applied to claims 1, 4, 6-10, 13-16, and 19 above, and further in view of Fine et al. (*Gen Comp Endocrin* (1993) 89:51-61). Claim 5 (in relevant part) is drawn to the method of claim 1 wherein the recombinant protein is carp growth hormone.

Hiramatsu et al. (1990) and Hiramatsu et al. (1989) disclose the teachings as described in items 14 and 15, respectively, above. The combined references of Hiramatsu et al. (1990) and Hiramatsu et al. (1989) do not teach a method for producing carp growth hormone (cGH).

Fine et al. teach the recombinant expression of cGH using *Escherichia coli* as an expression host (page 52, right column). Fine et al. teach the cDNA sequence of cGH has been isolated and characterized (page 52, left column, bottom to right column, top).

Also, at the time of the invention, one of ordinary skill in the art would have recognized the use and advantages of eukaryotic host cells over prokaryotic host cells for expression of eukaryotic proteins. Such advantages include post-translational modification such as glycosylation, which is known to affect in vivo protein activity, and phosphorylation.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Hiramatsu et al. (1990), Hiramatsu et al. (1989), and Fine et al. to practice the method as stated in item above for producing cGH using the vector of JGH2 with the nucleic acid encoding the five amino acid amino-terminal pro-peptide fragment replaced with a *full-length* MPR pro-peptide including an MPR pro-peptide-mature MPR cleavage site at the pro-peptide-hGH junction. One would have been motivated for a method for producing cGH using yeast instead of bacteria as an expression host in order to express cGH using a eukaryotic expression system because a eukaryotic expression system has obvious advantages in the expression of eukaryotic proteins as compared to a prokaryotic expression system as described above. One would have a reasonable expectation of success for a method of producing cGH using the vector of JGH2 with the nucleic acid encoding the five amino acid amino-terminal pro-peptide fragment replaced with a *full-length* MPR pro-peptide including an MPR pro-peptide-mature MPR cleavage site at the pro-peptide-cGH junction. Therefore, claim 5, drawn to the method of producing cGH as described above, would have been obvious to one of ordinary skill in the art.

[17] Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hiramatsu et al. in view of Fine et al. Claim 24 is drawn to the nucleic acid of claim 20, wherein the polypeptide is hirudin or carp growth hormone.

Hiramatsu et al. disclose the teachings as described in item above. The vectors of Hiramatsu et al. do not comprise a nucleic acid encoding carp growth hormone (cGH).

Fine et al. disclose the teachings as described in item 16 above.

Also, at the time of the invention, one of ordinary skill in the art would have recognized the use and advantages of eukaryotic host cells over prokaryotic host cells for expression of eukaryotic proteins. Such advantages include post-translational modification such as glycosylation, which is known to affect in vivo protein activity, and phosphorylation.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Hiramatsu et al. and Fine et al. to replace the nucleic acid encoding hGH of Hiramatsu et al. with a nucleic acid encoding cGH. One would have been motivated to replace the nucleic encoding hGH with cGH in order to express cGH using a eukaryotic expression system, which has obvious advantages in the expression of eukaryotic proteins as compared to a prokaryotic expression system. One would have a reasonable expectation of success for replacing the nucleic encoding hGH in the vectors of Hiramatsu et al. with a nucleic acid encoding cGH because of the teachings of Fine et al. Therefore, claim 24, drawn to the nucleic acid of claim 20, wherein the polypeptide is hirudin or carp growth hormone would have been obvious to one of ordinary skill in the art.

Conclusion

[18] Claims 1, 4-20, 24-26, 28-30, and 41-44 are rejected.

[19] Claim 27 is objected to.

[20] No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for official papers filed to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or

relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

MANJUNATH N. RAO
PATENT EXAMINER

Manjunath N. Rao, Ph.D.
Patent Examiner
Art Unit 1652